

Synthesis of novel scaffolds based on bis-thiazole linked to piperazine core as new hybrid molecules

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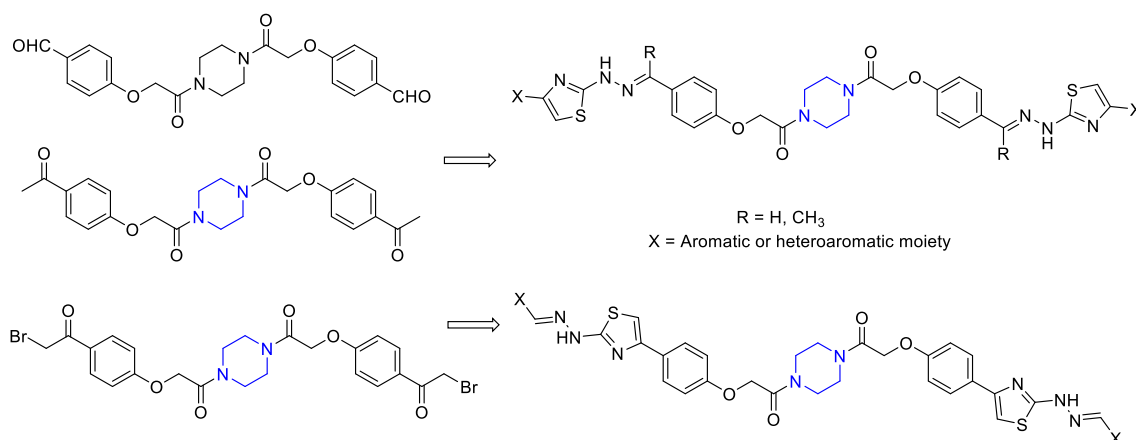
Received mm-dd-yyyy

Accepted Manuscript mm-dd-yyyy

Published on line mm-dd-yyyy

Abstract

Piperazine and thiazole moieties are commonly found in medicines and bioactive compounds. One of the fruitful ways in drug design is the hybridization of privilege structures in one skeleton, which are thought to provide a distinguishing feature with better or more selective biological activities than the two scaffolds. In this study, a series of bis-thiazoles, linked to piperazine as novel hybrid molecules, were synthesized in good yields by reacting the appropriate α -halo ketones or α -keto-hydrazoneyl chlorides with the corresponding piperazine bis(hydrazinecarbothioamide) in EtOH/DMF at reflux, in the presence of a few drops of TEA. The initial bis-thiosemicarbazones were formed by reacting the appropriate bis-aldehyde or bis-ethanone with thiosemicarbazide in EtOH with a few drops of AcOH at reflux. The novel compounds' structures were validated using elemental analysis and spectrum data.



Keywords: Bis-thiazoles, molecular hybridization, piperazine, bis(thiosemicarbazones), bis(α -bromoketones)

Cite as *Arkivoc* 2024 (8) 202412247

DOI: <https://doi.org/10.24820/ark.5550190.p012.247>

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Introduction

Studies have shown that the piperazine scaffold possesses antimalarial, anticancer, antibacterial, antituberculosis, antipsychotic, antiviral, antifungal, anti-Alzheimer's, analgesic, antidiabetic, and anticonvulsant characteristics.^{1–10} Figure 1 displays two drugs containing a piperazine core as a crucial structural element.

Additionally, thiazole-based frameworks are the most fascinating heterocycles in the field of synthetic medicinal chemistry due to their ease of chemical synthesis and structural refinement.¹¹ Furthermore, thiazoles display antidiabetic, antibacterial, anti-inflammatory, antiviral, antioxidant, anticancer, antiprotozoal, antifungal, and analgesic properties.^{12,13} Furthermore, they can be found in 18 FDA-approved medications, including meloxicam for anti-inflammatory purposes, tiazofurin and epothilone for antitumor treatment, febuxostat for antigout relief, isavuconazole as an antifungal, nizatidine and famotidine for antihistaminic use, thiabendazole and nitazoxanide for antiparasitic treatment, and sulfathiazole, aztreonam, ceftriaxone, cefepime, and edoxaban as antibacterial or anticoagulant options (Figure 1).^{14–16}

Additionally, over the past couple of decades, the concept of molecular hybridization has garnered significant attention in drug development. By combining two pharmacophoric components from different bioactive compound categories, this method creates new hybrid molecules that are both more potent and resilient in biological applications.^{17,18} Typically, lipophilicity is increased with larger molecule sizes compared to the original size. Hybridizing could result in safer and more efficient cancer drugs than those currently available.^{19,20}

It has been noted that many bis-heterocycles with the appropriate linker display antibacterial, anti-allergic, anticancer, and other disease-combating properties.^{21,22}

With these findings and our ongoing focus on creating bis(heterocycles) derivatives involving carbon-carbon bond formations^{23–42} we introduce the development and production of unique hybrid compounds comprised of bis(thiazoles) linked to piperazine.

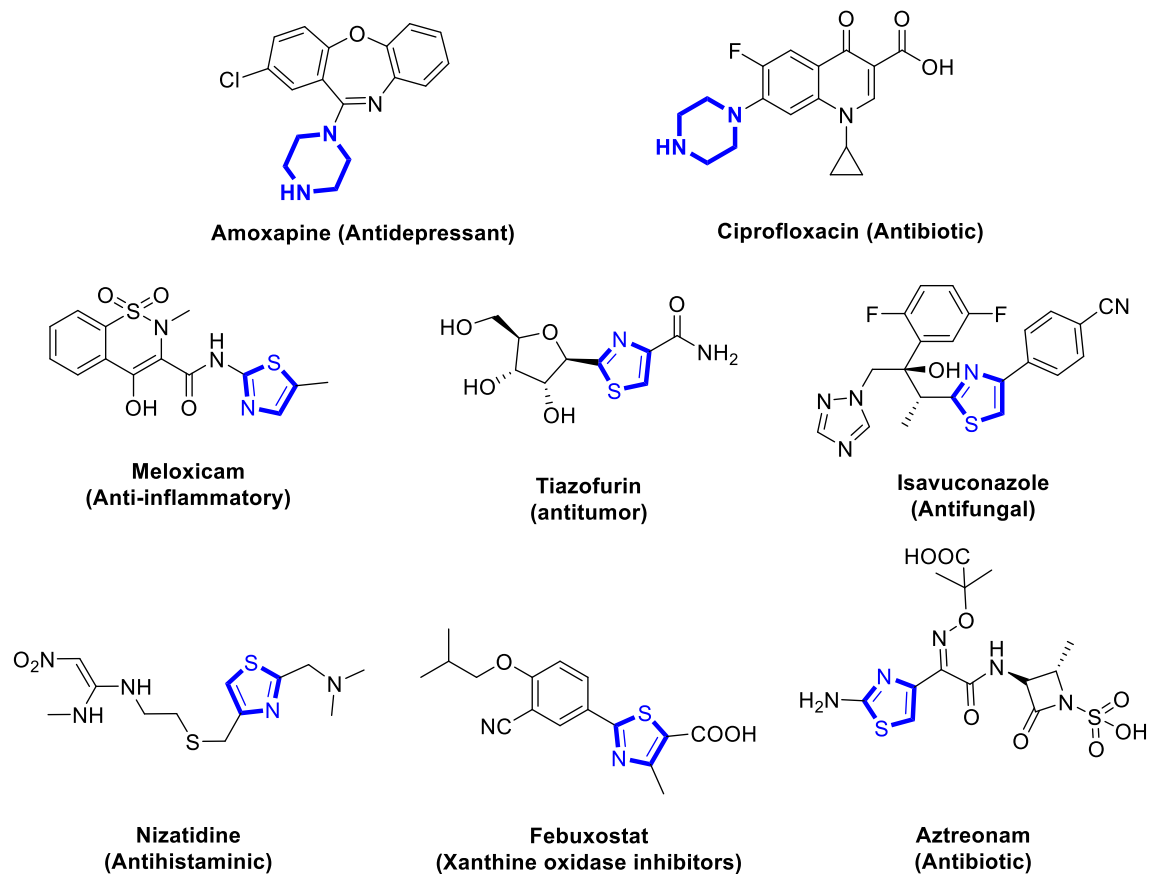
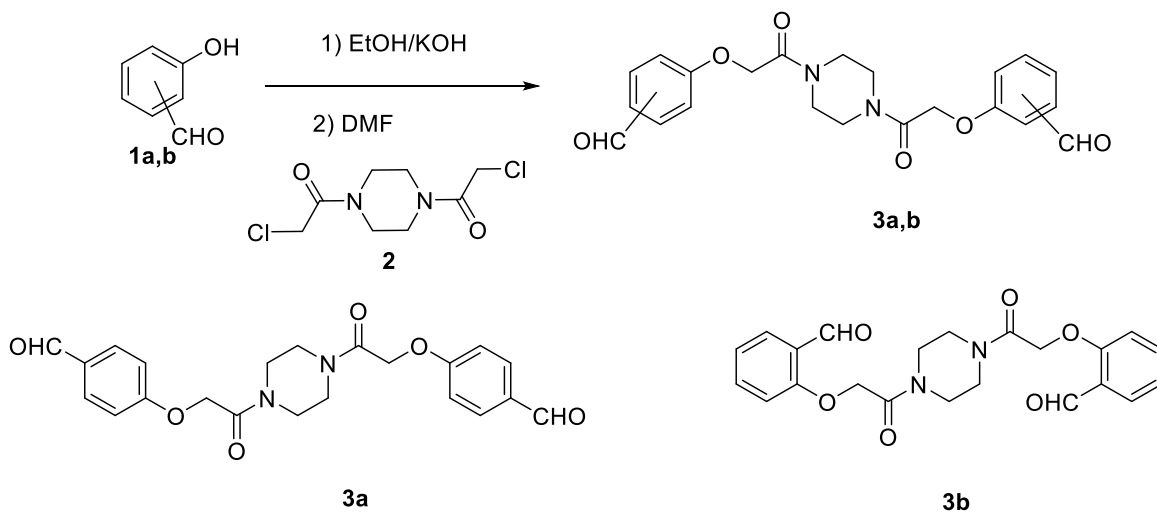


Figure 1: Some clinically approved drugs (FDA-approved) including piperazine or thiazole ring moiety

Results and Discussion

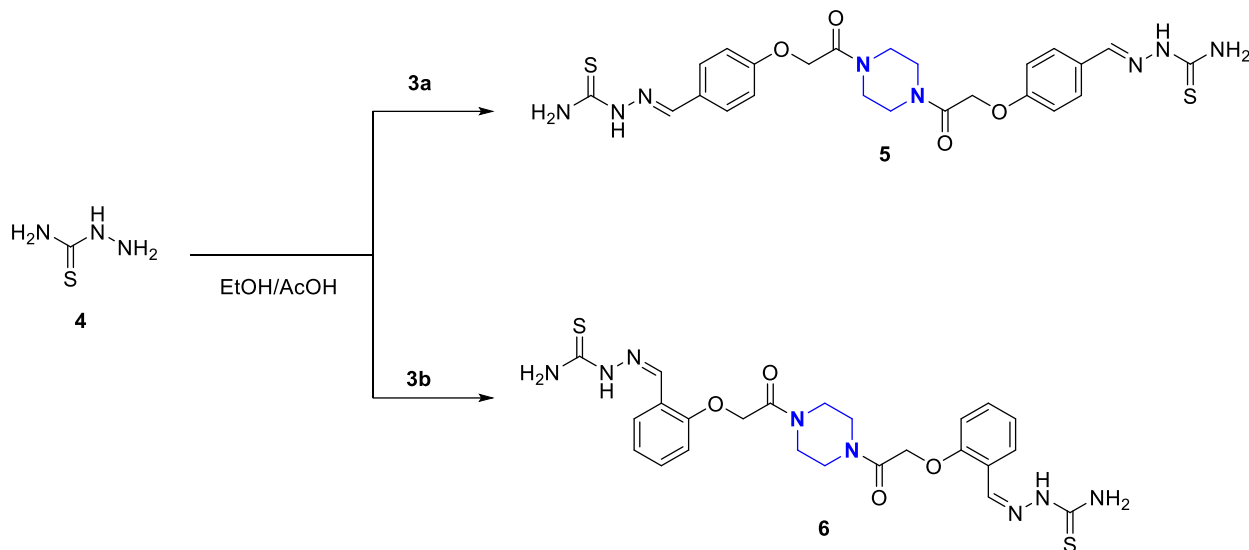
Synthesis

Bis-aldehydes **3a** and **3b** were prepared in good yields by reacting 1,1'-(piperazine-1,4-diyl)bis(2-chloroethan-1-one) **2** with potassium salts of salicylaldehyde **1a**, and *p*-hydroxybenzaldehyde **1b** (Scheme 1) in DMF at reflux.⁴³



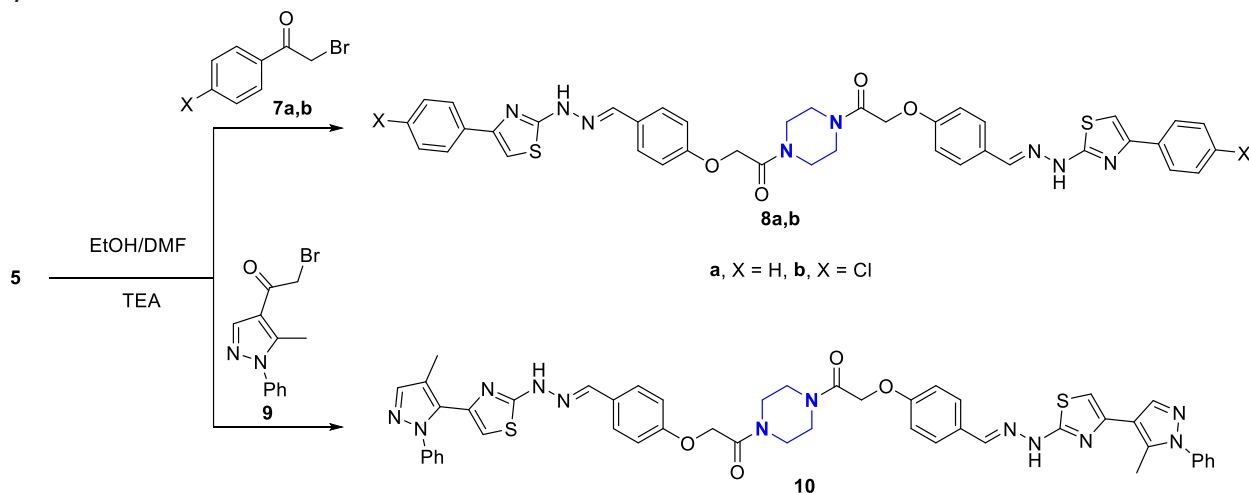
Scheme 1 Synthesis of bis-aldehydes **3a** and **3b**

The novel bis(thiosemicarbazones) **5** and **6** were effectively synthesized in 83 and 79% yields, respectively, from bis-aldehydes **3a** and **3b** by reacting them with thiosemicarbazide (**4**) in refluxing EtOH containing a few drops of AcOH.



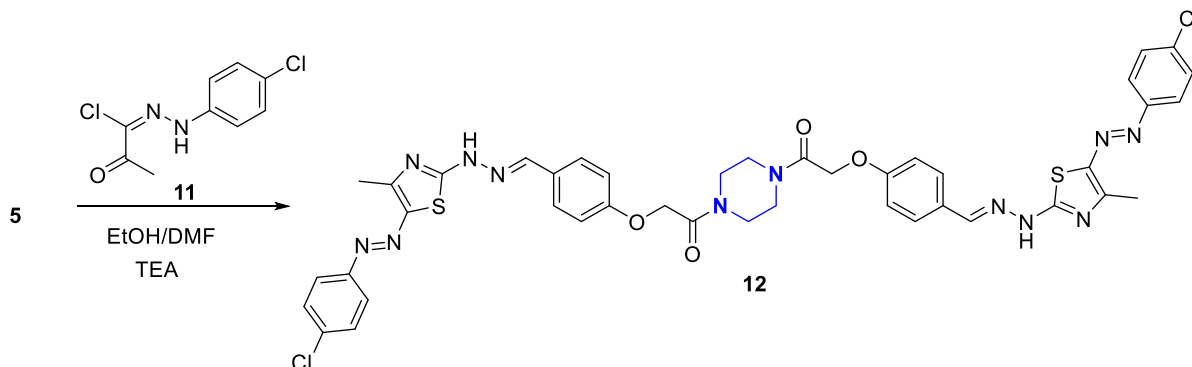
Scheme 2 Synthesis of bis(thiosemicarbazones) **5** and **6**

Bis(thiosemicarbazones) **5** and **6** were utilized as intermediates in the synthesis of novel bis(thiazoles). Thus, the reaction of **5** with phenacyl bromide (**7a**) and 2-bromo-1-(4-chlorophenyl)ethenone (**7b**) in ethanol/DMF mixture at reflux in the presence of a few drops of TEA, led to the formation of bis(4-arylthiazoles) **8a** and **8b** in which (thiazol-2-yl)hydrazineylidene are linked to the piperazine core via the phenoxyacetyl linker in 85% and 88% yields, respectively (Scheme 3). Similarly, the reaction of **5** with 2-bromo-1-(5-methyl-1-phenyl-1H-pyrazol-4-yl)ethanone (**9**) yielded bis(1H-pyrazol-5-yl)thiazole **10** in which (1H-pyrazol-5-yl)thiazol-2-yl)hydrazineylidene is linked to the piperazine core via the phenoxyacetyl linker in 78% yield (Scheme 3). Compound **10** represents an intriguing hybrid molecule with three distinct bioactive heterocyclic moieties.



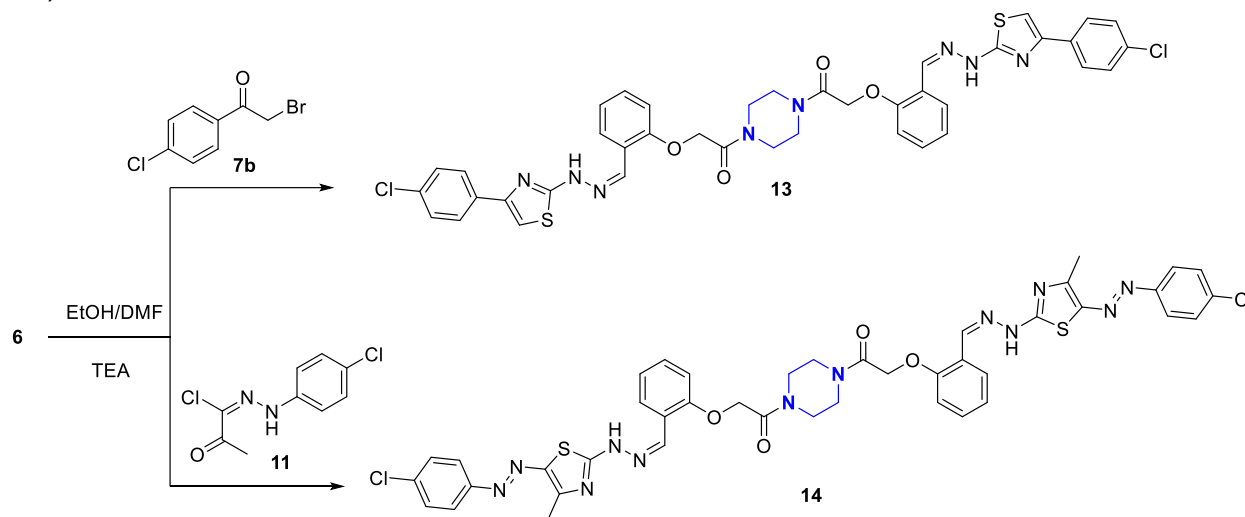
Scheme 3 Synthesis of bis(4-thiazoles) **8a**, **8b**, and **10**

Similarly, in the presence of TEA as a catalyst, the reaction of the bis(hydrazinecarbothioamide) **5** with the corresponding α -keto-hydrazoneyl chloride **11** ethanol/DMF mixture at reflux yielded the corresponding bis(thiazole) **12** in which (4-chlorophenyl)diazenylthiazol-2-ylhydrazineylidene is linked to the piperazine core via the phenoxyacetyl linker in 85% yield (Scheme 4).



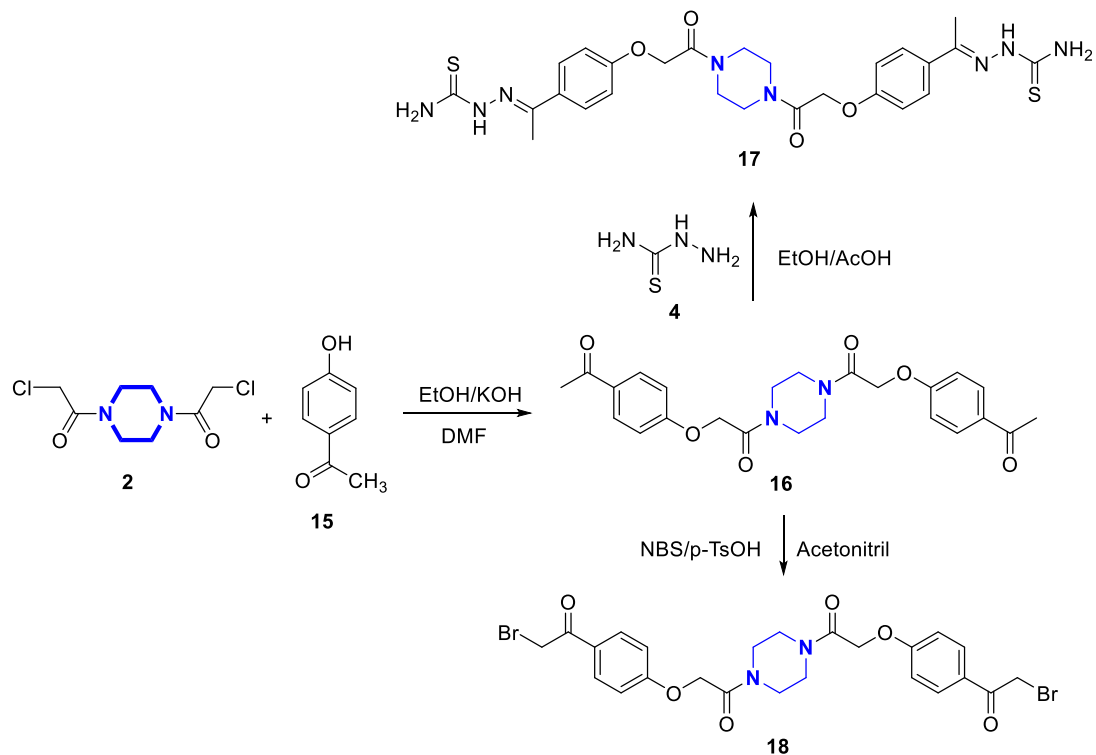
Scheme 4 Synthesis of bis[5-(4-chlorophenyldiazenyl)thiazole] **12**

The evaluation of the reaction's generality involved the synthesis of bis(thiazoles) **13** and **14** in 79 and 91% yields, respectively, through the reaction of the bis(hydrazinecarbothioamide) **6** with N-(4-chlorophenyl)-2-oxopropanehydrazoneyl chloride **11** and 2-bromo-1-(4-chlorophenyl)ethenone (**7b**) under comparable conditions, as illustrated in Scheme 5.



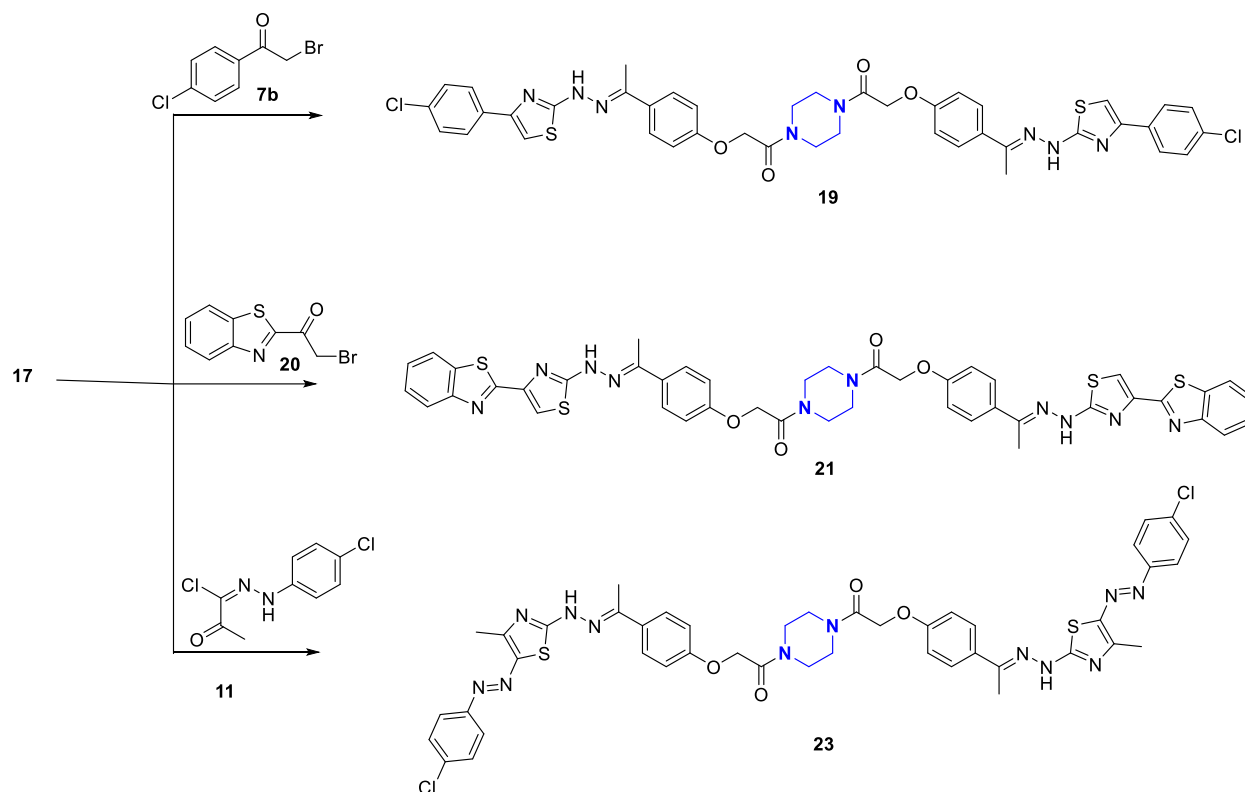
Scheme 5 Synthesis of bis(thiazoles) **13**, and **14**

By reacting 1,1'-(piperazine-1,4-diyl)bis(2-chloroethan-1-one) (**2**) with the potassium salt of *p*-hydroxy acetophenone (**15**) in DMF at reflux, 1,1'-(piperazine-1,4-diyl)bis(2-(4-acetylphenoxy)ethan-1-one) **16** was effectively produced in a 79% yield (Scheme 6). The equivalent bis(hydrazinecarbothioamide) **17** was produced by the reaction of **16** with thiosemicarbazide (**4**) in refluxing EtOH containing a few drops of AcOH. In a 71% yield, 1,1'-(Piperazine-1,4-diyl)bis(2-(4-(2-bromoacetyl)phenoxy)ethan-1-one) **18** was produced by reacting **16** with N-bromosuccinimide in acetonitrile at reflux while *p*-toluenesulfonic acid (PTSA) was present as a catalyst (Scheme 6).²⁵



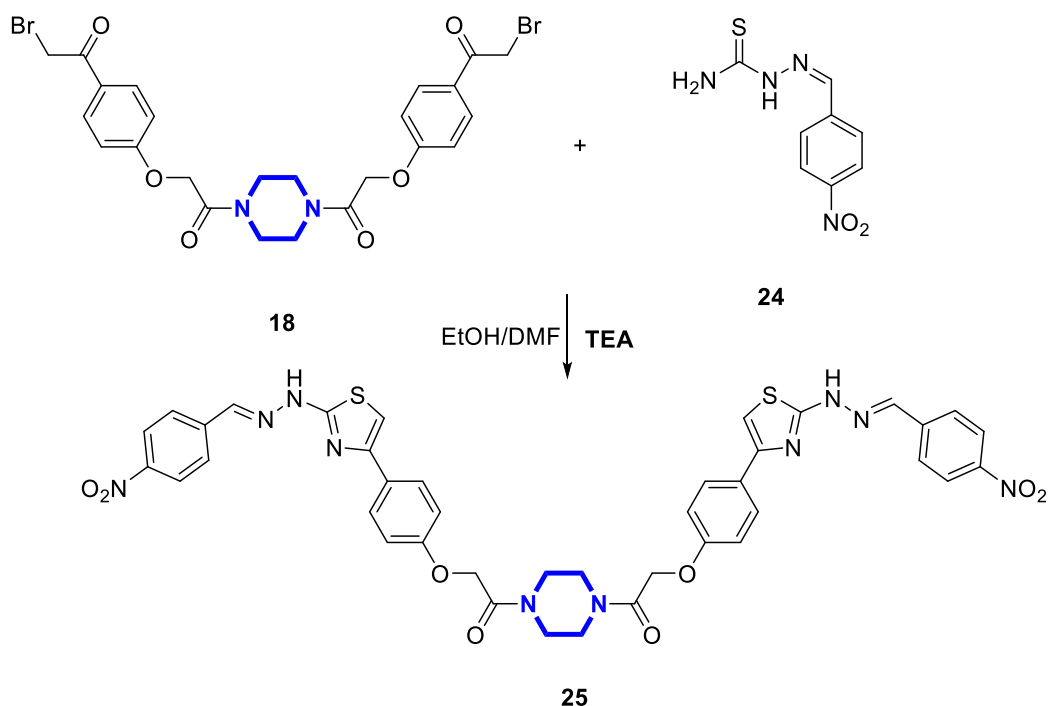
Scheme 6 Synthesis of bis(acetylphenoxyethan-1-one) **16**, bis(hydrazinecarbothioamide) **17**, and bis(bromoacetylphenoxyethan-1-one) **18**

The potential of bis(hydrazinecarbothioamide) **17** as a precursor for new bis-thiazoles was also explored. Bis-thiazoles **19**, **21**, and **23** can be produced in 87, 85, and 83 % yields, respectively, by the reaction of **17** with 2-bromo-1-(4-chlorophenyl)ethenone (**7b**), 1-(benzo[*d*]thiazol-2-yl)-2-bromoethanone (**20**), and α -keto-hydrazonoyl chloride **11** in refluxing ethanol/DMF mixture in the presence of TEA resulted (Scheme 7).



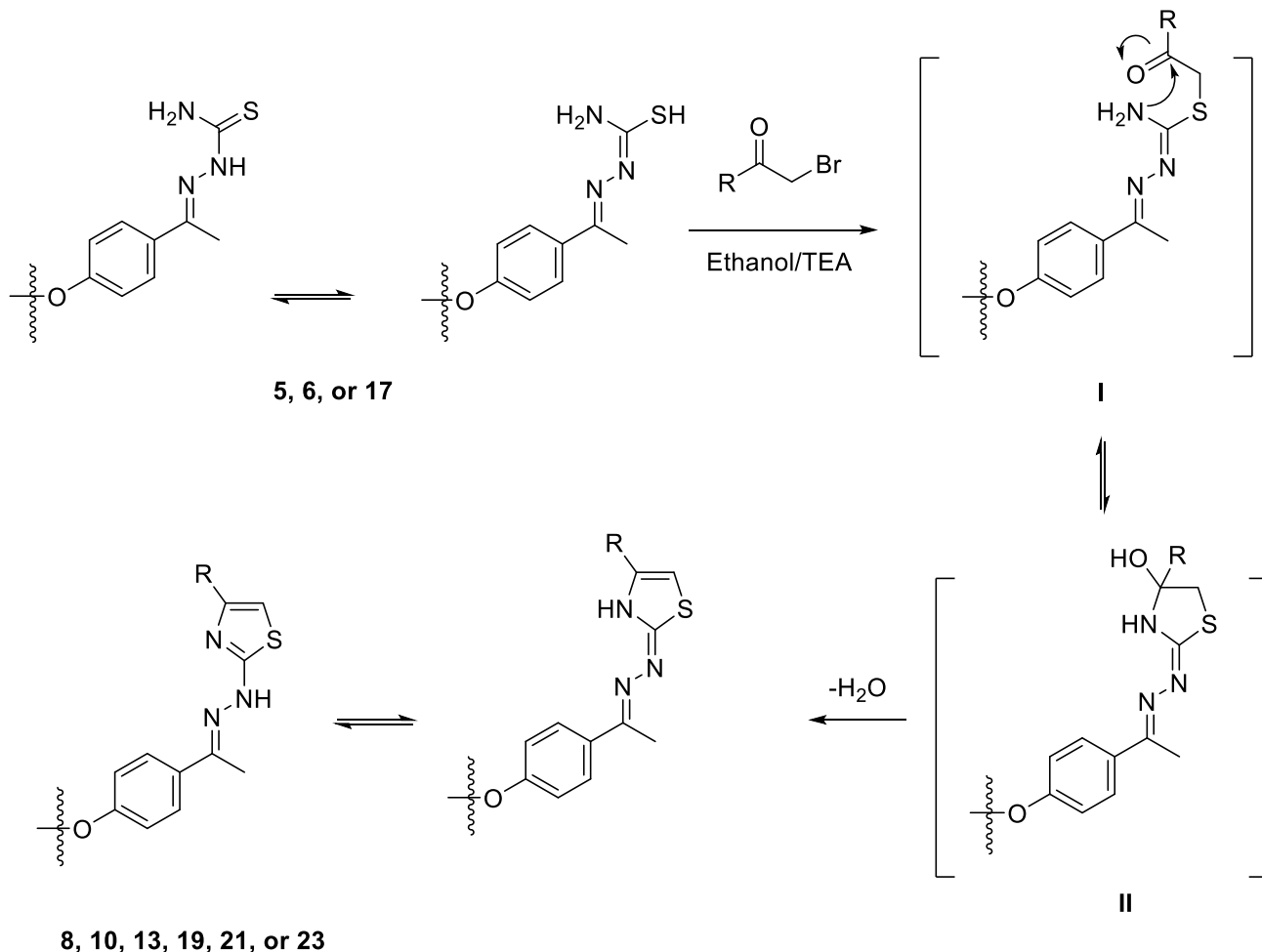
Scheme 7 Synthesis of bis(thiazoles) **19**, **21**, and **23**

In Scheme 8, 1,1'-(piperazine-1,4-diyl)bis(2-(4-(2-(2-(4-nitrobenzylidene)hydrazineyl)thiazol-4-yl)phenoxy)ethan-1-one) (**25**) was synthesized by reacting bis(α -bromoketone) **18** with 2-(4-nitrobenzylidene)hydrazine-1-carbothioamide **24** in a refluxing EtOH/DMF mixture containing a few drops of TEA.



Scheme 8 Synthesis of bis(thiazole) **25**

In Scheme 9, we propose that the formation of bis-thiazoles begins with the formation of non-isolable intermediates I through *S*-alkylation of the appropriate hydrazinecarbothioamides **5**, **6**, or **17** with the corresponding α -bromoketones, and hydrogen bromide is removed to yield *S*-alkylated intermediates I. The latter underwent sequential in situ cyclization to the respective non-isolable intermediates II, which, following the loss of water molecules under the experimental circumstances, gave the desired bis-thiazoles **8a,b**, **10**, **13**, **19**, **21**, or **23** as the end condensation products.



Scheme 9 A plausible mechanism for the formation of the target bis-thiazoles

Spectroscopy

All isolated products were characterized using elemental analysis and spectrum data, which agree with the predicted structures. The IR spectrum of **8a**, a sample example, revealed absorption bands at 3250 cm^{-1} and 1659 cm^{-1} due to NH and CO stretching frequencies. The ^1H NMR spectrum revealed a D_2O -exchangeable signal at δ 12.04 attributable to NH protons and a distinctive singlet signal at δ 7.27 ascribed to C-5 protons in the thiazole ring. They also included the methylene ether linkage OCH_2 as a singlet signal at δ 4.91 ppm. The piperazine showed wide signals at δ 3.45-3.53. All additional protons were detected with the predicted chemical shifts and integral values. Compound **8a**'s mass spectrum revealed the expected molecular ion peak at m/z 756. The IR spectra of **14** showed absorption bands at 3233 cm^{-1} from NH groups and 1661 cm^{-1} from CO groups. The mass spectra also showed predicted molecular ion peaks at m/z 908. The ^1H NMR spectra of **23** revealed a D_2O -exchangeable signal at δ 10.57 due to NH protons, as well as acute singlet signals at 2.44, 2.52,

and 5.00 ppm attributable to 4-CH₃ of the thiazole group, CH₃ of the hydrazone group, and OCH₂ of the linker, respectively. Piperazine-related signals and aromatic protons occurred in the predicted sites.

Conclusions

Molecular hybridization has lately emerged as a highly effective drug discovery strategy. In this work, we designed and synthesized a new family of bis(thiazoles) that are connected to piperazine via the phenoxyacetyl group. As hybrid molecules with two separate pharmacophores, the newly synthesized compounds are likely to have diverse biological roles and dual activity. The simple synthesis of these compounds in high yields under mild reaction conditions using readily available starting materials may open the way for novel bis(functionalized) heterocycles with predicted biological and pharmacological properties.

Experimental Section

General. Melting points were measured with a Stuart melting point apparatus and were uncorrected. The IR spectra were recorded using an FTIR Bruker-vector 22 spectrophotometer as KBr pellets. The ¹H and ¹³C NMR spectra were recorded in DMSO-*d*₆ as a solvent with a Varian Mercury VXR-300 NMR spectrometer operating at 300 MHz for ¹H NMR and 75 MHz for ¹³C NMR or on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ¹H NMR, and 125.65 MHz for ¹³C NMR using TMS as an internal standard. Chemical shifts were reported as δ values in ppm. Mass spectra were recorded with a Shimadzu GCMS-QP-1000 EX mass spectrometer in an EI (70 eV) model. The elemental analyses were performed at the Microanalytical Centre, Cairo University

General procedure for the synthesis of compounds 3a and 3b. Salicylaldehyde **1a**, or *p*-hydroxybenzaldehyde **1b** (10 mmol) was dissolved in hot ethanolic KOH solution (prepared by dissolving 0.56 g (10 mmol) of KOH in 10 mL of absolute ethanol), and the solvent was then removed in vacuo. The remaining material was dissolved in DMF (10 mL) and 1,1'-(piperazine-1,4-diyl)bis(2-chloroethan-1-one) (**2**) (5 mmol) was added. The reaction mixture was refluxed for 10 min. during which KCl was separated. The solvent was then removed in vacuo and the remaining materials were poured onto crushed ice. The crude products recrystallized from the proper solvent to give **3a** and **3b**, respectively.

4,4'-((Piperazine-1,4-diyl)bis(2-oxoethane-2,1-diyl))bis(oxy)dibenzaldehyde (3a). Colorless solid (Ethanol/Acetic acid), (94%), mp 190-192 °C; IR (KBr, ν cm⁻¹): 2865, 2744 (aldehyde CH), 1664 (CO). ¹H NMR (300 MHz, DMSO-*d*₆): δ 3.5 (d, 8H, -NCH₂-), 5.04 (s, 4H, -OCH₂-), 7.12 (d, 4H, Ar-H, *J* 9 Hz), 7.85 (d, 4H, Ar-H, *J* 8.7 Hz), 9.87 (s, 2H, -CHO); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 43.9, 65.8, 115.2, 129.8, 131.6, 163.1, 165.5, 191.3; MS: *m/z* (%) 410 [M]⁺. Anal. Calcd. For C₂₂H₂₂N₂O₆: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.37; H, 5.42; N, 6.87%.

2,2'-((Piperazine-1,4-diyl)bis(2-oxoethane-2,1-diyl))bis(oxy)dibenzaldehyde (3b). Colorless solid (Ethanol/DMF), (90% yield), mp 254-256 °C; IR (KBr, ν cm⁻¹): 2874, 2771 (aldehyde CH), 1651 (aldehyde CO), 1599 (amide CO); ¹H NMR (300 MHz, DMSO-*d*₆): δ 3.5 (d, 8H, -NCH₂-), 5.11 (s, 4H, -OCH₂-), 7.07-7.19 (m, 4H, Ar-H), 7.63-7.73 (m, 4H, Ar-H), 10.46 (s, 2H, -CHO). MS: *m/z* (%) 410 [M]⁺. Anal. Calcd. For C₂₂H₂₂N₂O₆: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.42; H, 5.37; N, 6.89%.

Synthesis of bis(2-arylidenehydrazine-1-carbothioamides) 5 and 6. To a solution of the piperazine bis(aldehyde) compound **3a,b** (10 mmol) in absolute ethanol (25 mL) containing 1 ml of acetic acid, thiosemicarbazide (**4**) (20 mmol) was added. The reaction mixture was heated under reflux for 3 h and then cooled. The solid formed was collected by filtration and recrystallized from ethanol/DMF to give **5,6** as Paige powder.

2,2'-((((Piperazine-1,4-diylbis(2-oxoethane-2,1-diyl))bis(oxy))bis(4,1-phenylene))

bis(methaneylylidene))bis(hydrazine-1-carbothioamide (5). Paige powder (83%), mp 222-224 °C; IR (cm⁻¹): 3409, 3292 (NH₂), 3150 (NH), 1665 (C=O); ¹H-NMR (DMSO): δ 3.47 (d, 8H, -NCH₂-), 4.90 (s, 4H, -OCH₂-), 6.92 (d, *J* 8.5 Hz, 4H, ArH), 7.69 (d, *J* 8.5 Hz, 4H, ArH), 7.91 (s, 4H, NH₂), 8.12 (s, 2H, CH=N), 11.23 (s, 2H, NH); ¹³C-NMR: δ 47.4, 68.7, 116.2, 126.5, 130.2, 146.9, 160.4, 166.4, 178.2; MS: *m/z* (%) 556 (M⁺). Anal. Calcd. For C₂₄H₂₈N₈O₄S₂: C, 51.78; H, 5.07; N, 20.13; S, 11.52. Found: C, 51.73; H, 5.06; N, 20.11; S, 11.53%

2,2'-((((Piperazine-1,4-diylbis(2-oxoethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))

bis(methaneylylidene))bis(hydrazine-1-carbothioamide (6). Paige powder (79%), mp 211-213 °C; IR (cm⁻¹): 3423, 3297 (NH₂), 3133 (NH), 1661 (C=O); ¹H-NMR (DMSO): δ 3.49 (d, 8H, -NCH₂-), 4.95 (s, 4H, -OCH₂-), 7.00 (s, 4H, NH₂), 7.62-7.82 (m, 8H, ArH), 8.10 (s, 2H, CH=N), 11.14 (s, 2H, NH); MS: *m/z* (%) 556 (M⁺). Anal. Calcd. For C₂₄H₂₈N₈O₄S₂: C, 51.78; H, 5.07; N, 20.13; S, 11.52. Found: C, 51.73; H, 5.06; N, 20.11; S, 11.53%.

Synthesis of bis(thiazoles) 8a, 8b, 10, and 13

General procedure. A mixture of the appropriate 2-bromoethanone derivatives (2 mmol) with the bis(aldehydethiosemicarbazone) **5** or **6** (1 mmol) was dissolved in ethanol (25 mL), TEA (0.2 mL) was added, and the reaction mixture was heated at reflux for 3-5 h. The reaction mixture was then left to cool, the solid product was filtered off and recrystallized from ethanol/DMF, to afford compounds **8a, 8b, 10, and 13**.

1,1'-(Piperazine-1,4-diyl)bis(2-(4-(2-(4-phenylthiazol-2-yl)hydrazineylidene) methyl) phenoxy)ethan-1-one (8a). Creamy powder (85%), mp 266-268 °C; IR (cm⁻¹): 3250 (NH), 1659 (C=O); ¹H-NMR (DMSO): δ 3.49 (d, 8H, -NCH₂-), 4.91 (s, 4H, -OCH₂-), 6.97 (d, *J* 8.5 Hz, 4H, ArH), 7.27 (s, 2H, thiazole-5-H), 7.28-7.57 (m, 10H, ArH), 7.82 (d, *J* 8.5 Hz, 4H, ArH), 7.95 (s, 2H, CH=N), 12.04 (s, 2H, NH); MS: *m/z* (%) 756 (M⁺). Anal. Calcd. For C₄₀H₃₆N₈O₄S₂: C, 63.47; H, 4.79; N, 14.80; S, 8.47. Found: C, 63.48; H, 4.76; N, 14.77; S, 8.49%.

1,1'-(Piperazine-1,4-diyl)bis(2-(4-(2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazineylidene)

methyl)phenoxy)ethan-1-one (8b). Yellow crystal (88%), mp 285-287 °C; IR (cm⁻¹): 3256 (NH), 1655 (C=O); ¹H-NMR (DMSO): δ 3.49 (d, 8H, -NCH₂-), 4.90 (s, 4H, -OCH₂-), 6.97 (d, *J* 8.5 Hz, 4H, ArH), 7.34 (s, 2H, thiazole-5-H), 7.41-7.57 (m, 8H, ArH), 7.83 (d, *J* 8.5 Hz, 4H, ArH), 7.95 (s, 2H, CH=N), 12.03 (s, 2H, NH); ¹³C-NMR: δ 45.5, 68.6, 104.0, 115.9, 126.2, 127.6, 129.4, 130.3, 136.3, 143.6, 150.0, 160.7, 167.1, 179.3; MS: *m/z* (%) 825 (M⁺). Anal. Calcd. For C₄₀H₃₄Cl₂N₈O₄S₂: C, 58.18; H, 4.15; N, 13.57; S, 7.76. Found: C, 58.15; H, 4.11; N, 13.59; S, 7.73%.

2-(4-(2-(4-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)hydrazineylidene)methyl)-phenoxy)-1-(4-(2-(4-(2-(4-(4-methyl-1-phenyl-1H-pyrazol-5-yl)thiazol-2-yl)hydrazineylidene)-methyl)phenoxy)acetyl)piperazin-1-yl)ethan-1-one (10). Brown powder (78%), mp 244-246 °C; IR (cm⁻¹): 3229 (NH), 1665 (C=O); ¹H-NMR (DMSO): δ 2.50 (s, 6H, CH₃), δ 3.49 (d, 8H, -NCH₂-), 4.91 (s, 4H, -OCH₂-), 6.84-6.96 (m, 6H, ArH), 7.42 (s, 2H, thiazole-5-H), 7.43-7.56 (m, 12H, ArH), 7.90 (s, 2H, CH=N), 7.94 (s, 2H, pyrazole-3-H), 12.00 (s, 2H, NH); ¹³C-NMR: δ 18.5, 44.7, 67.0, 104.7, 105.2, 115.6, 117.0, 125.0, 126.4, 129.3, 131.0, 134.1, 135.1, 143.3, 149.0, 161.4, 167.3, 177.8; MS: *m/z* (%) 917 (M⁺). Anal. Calcd. For C₄₈H₄₄N₁₂O₄S₂: C, 62.87; H, 4.84; N, 18.33; S, 6.99. Found: C, 62.84; H, 4.81; N, 18.31; S, 6.91%.

1,1'-(Piperazine-1,4-diyl)bis(2-(2-((2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazineylidene)

methyl)phenoxy)ethan-1-one) (13). Creamy powder (80%), mp 230-233 °C; IR (cm⁻¹): 3224 (NH), 1653 (C=O); ¹H-NMR (DMSO): δ 3.50 (d, 8H, -NCH₂-), 4.98 (s, 4H, -OCH₂-), 6.94-6.98 (m, 8H, ArH), 7.36 (s, 2H, thiazole-5-H), 7.42 (d, *J* 7.5 Hz, 4H, ArH), 7.83 (d, *J* 8 Hz, 4H, ArH), 8.38 (s, 2H, CH=N), 12.22 (s, 2H, NH); MS: *m/z* (%) 825 (M⁺). Anal. Calcd. For C₄₀H₃₄Cl₂N₈O₄S₂: C, 58.18; H, 4.15; N, 13.57; S, 7.76. Found: C, 58.15; H, 4.11; N, 13.59; S, 7.73%.

Synthesis of bis(thiazoles) 12 and 14. To a solution of the bis(thiosemicarbazone) **5** or **6**, in ethanol (25mL) containing TEA (0.2 ml) the appropriate α-ketohydrazoneyl chlorides **11** (2 mmol) was added. The reaction mixture was heated under reflux for 5 h. The solvent was then evaporated in vacuo, and the solid residues were collected by filtration and recrystallized from ethanol/DMF to give compounds **12** and **14**.

1,1'-(Piperazine-1,4-diyl)bis(2-(4-((2-(5-((4-chlorophenyl)diazenyl)-4-methylthiazol-2-

yl)hydrazineylidene)methyl)phenoxy)ethan-1-one) (12). Orange crystal (85%), mp 260-262 °C; IR (cm⁻¹): 3233 (NH), 1661 (C=O); ¹H-NMR (DMSO): δ 2.54 (s, 6H, CH₃), 3.50 (d, 8H, -NCH₂-), 4.97 (s, 4H, -OCH₂-), 7.05 (d, *J* 8 Hz, 4H, ArH), 7.33 (s, 8H, ArH), 7.78 (d, *J* 7.5 Hz, 4H, ArH), 8.59 (s, 2H, CH=N), 10.61 (s, 2H, NH); ¹³C-NMR: δ 17.0, 44.4, 66.3, 115.7, 116.2, 126.2, 127.3, 129.7, 130.5, 139.3, 142.9, 149.2, 160.4, 161.4, 166.3, 178.6; MS: *m/z* (%) 908 (M⁺). Anal. Calcd. For C₄₂H₃₈Cl₂N₁₂O₄S₂: C, 55.44; H, 4.21; N, 18.47; S, 7.05. Found: C, 55.44; H, 4.23; N, 18.45; S, 7.02%.

1,1'-(Piperazine-1,4-diyl)bis(2-(2-((2-(5-((4-chlorophenyl)diazenyl)-4-methylthiazol-2-yl)-

hydrazineylidene)methyl)phenoxy)ethan-1-one) (14). Orange crystal (78%), mp 242-244 °C; IR (cm⁻¹): 3229 (NH), 1663 (C=O); ¹H-NMR (DMSO): δ 2.55 (s, 6H, CH₃), 3.49 (d, 8H, -NCH₂-), 4.94 (s, 4H, -OCH₂-), 6.93 (d, *J* 7.5 Hz, 4H, ArH), 7.29-7.34 (m, 4H, ArH), 7.91-8.15 (m, 8H, ArH), 8.40 (s, 2H, CH=N), 11.49 (s, 2H, NH); MS: *m/z* (%) 908 (M⁺). Anal. Calcd. For C₄₂H₃₈Cl₂N₁₂O₄S₂: C, 55.44; H, 4.21; N, 18.47; S, 7.05. Found: C, 55.44; H, 4.23; N, 18.45; S, 7.02%.

Synthesis of 1,1'-(piperazine-1,4-diyl)bis(2-acetylphenoxy)ethanone) derivative 16.

4-Hydroxyacetophenone **15** (10 mmol) was dissolved in hot ethanolic KOH solution (prepared by dissolving 0.56 g (10 mmol) of KOH in 10 mL of absolute ethanol), and the solvent was then removed in vacuo. The remaining material was dissolved in DMF (10 mL) and 1,1'-(piperazine-1,4-diyl)bis(2-chloroethan-1-one) (**2**) (5 mmol) was added. The reaction mixture was refluxed for 10 min. during which KCl was separated. The solvent was then removed in vacuo and the remaining materials were poured onto crushed ice. The crude product was recrystallized from DMF **1** as colorless crystals (79%), mp 240 °C; IR (KBr) 1698 (C=O), 1677 (C=O) cm⁻¹; ¹H-NMR: δ 2.51 (s, 6H, CH₃), 3.51 (d, 8H, NCH₂), 5.00 (s, 4H, OCH₂), 7.02 (d, *J* 8.7 Hz, 4H, ArH), 7.91 (d, *J* 8.7 Hz, 4H, ArH); MS: *m/z* (%) 438 (M⁺). Anal. Calcd. for C₂₄H₂₆N₂O₆; C, 65.74; H, 5.98; N, 6.39. Found: C, 65.71; H, 5.97; N, 6.38%.

Synthesis of 2,2'-((((piperazine-1,4-diyl)bis(2-oxoethane-2,1-diyl))bis(oxy))bis(4,1-phenylene))bis(ethan-1-yl-

1-ylidene))bis(hydrazine-1-carbothioamide) (17). To a solution of the piperazine bis(acetyl) compound **16** (10 mmol) in absolute ethanol (25 mL) containing 1 ml of acetic acid, thiosemicarbazide (**4**) (20 mmol) was added. The reaction mixture was heated under reflux for 3 h and then cooled. The solid formed was collected by filtration and recrystallized from ethanol/DMF to give **17** as a creamy powder (80%), mp 212-214 °C; IR (cm⁻¹): 3415, 3295 (NH₂), 3158 (NH), 1664 (C=O); ¹H-NMR (DMSO): δ 2.26 (s, 6H, CH₃), 3.50 (d, 8H, -NCH₂-), 4.91 (s, 4H, -OCH₂-), 6.92 (d, *J* 9 Hz, 4H, ArH), 7.71 (s, 4H, NH₂), 7.86 (d, *J* 9 Hz, 4H, ArH), 10.09 (s, 2H, NH); MS: *m/z* (%) 584 (M⁺). Anal. Calcd. For C₂₆H₃₂N₈O₄S₂: C, 53.41; H, 5.52; N, 19.16; S, 10.97. Found: C, 53.41; H, 5.50; N, 19.17; S, 10.98%.

Synthesis of bis(thiazoles) 19, 21, and 23. A mixture of the appropriate 2-bromoethanone or α -keto-hydrazone derivatives (2 mmol) with the bis(acetylthiosemicarbazone) **17** (1 mmol) was dissolved in ethanol (25 mL), TEA (0.2 mL) was added, and the reaction mixture was heated at reflux for 3-5 h. The reaction mixture was then left to cool, and the solid product was filtered off and recrystallized from ethanol/DMF, to afford compounds **19**, **21**, and **23**.

1,1'-(Piperazine-1,4-diyl)bis(2-(4-(1-(2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazineylidene)ethyl)phenoxy)ethan-1-one) (19). Brown powder (87%), mp 255-257 °C; IR (cm⁻¹): 3250 (NH), 1663 (C=O); ¹H-NMR (DMSO): δ 2.26 (s, 6H, CH₃), 3.50 (d, 8H, -NCH₂-), 4.90 (s, 4H, -OCH₂-), 6.95 (d, *J* 7 Hz, 4H, ArH), 7.35 (s, 2H, thiazole-5-H), 7.43 (d, *J* 8 Hz, 4H, ArH), 7.68 (d, *J* 7 Hz, 4H, ArH), 7.85 (d, *J* 7.5 Hz, 4H, ArH), 11.14 (s, 2H, NH); ¹³C-NMR: δ 19.4, 44.0, 67.3, 104.0, 116.4, 126.5, 127.0, 129.3, 130.9, 139.7, 142.5, 148.0, 160.1, 161.8, 166.0, 172.9; MS: *m/z* (%) 852 (M⁺). Anal. Calcd. For C₄₂H₃₈Cl₂N₈O₄S₂: C, 59.08; H, 4.49; N, 13.12; S, 7.51. Found: C, 59.08; H, 4.46; N, 13.11; S, 7.51%.

1,1'-(Piperazine-1,4-diyl)bis(2-(4-(1-(2-(4-(benzo[d]thiazol-2-yl)thiazol-2-yl)hydrazineylidene)ethyl)phenoxy)ethan-1-one) (21). Yellow powder (85%), mp 247-249 °C; IR (cm⁻¹): 3275 (NH), 1661 (C=O); ¹H-NMR (DMSO): δ 2.32 (s, 6H, CH₃), 3.53 (d, 8H, -NCH₂-), 4.93 (s, 4H, -OCH₂-), 6.98-8.11 (m, 18H, ArH and thiazole-5-H), 11.40 (s, 2H, NH); MS: *m/z* (%) 898 (M⁺). Anal. Calcd. For C₄₄H₃₈N₁₀O₄S₄: C, 58.78; H, 4.26; N, 15.58; S, 14.26. Found: C, 58.77; H, 4.25; N, 15.58; S, 14.25%.

1,1'-(Piperazine-1,4-diyl)bis(2-(4-(1-(2-(5-((4-chlorophenyl)diazenyl)-4-methylthiazol-2-yl)hydrazineylidene)ethyl)phenoxy)ethan-1-one) (23). Orange powder (83%), mp 270-272 °C; IR (cm⁻¹): 3290 (NH), 1659 (C=O); ¹H-NMR (DMSO): δ 2.44 (s, 6H, CH₃), 2.52 (s, 6H, CH₃), 3.50 (d, 8H, -NCH₂-), 5.00 (s, 4H, -OCH₂-), 7.01-7.90 (m, 16H, ArH), 10.57 (s, 2H, NH); MS: *m/z* (%) 936 (M⁺). Anal. Calcd. For C₄₄H₄₂Cl₂N₁₂O₄S₂: C, 56.35; H, 4.51; N, 17.92; S, 6.84. Found: C, 56.33; H, 4.52; N, 17.92; S, 6.81 %.

Synthesis of 1,1'-(piperazine-1,4-diyl)bis(2-(4-(2-bromoacetyl)phenoxy)ethan-1-one) 18. To a stirred solution of the bis(acetophenone) derivative **16** (10 mmol) and *p*-TsOH (5.6 g, 20 mmol) in acetonitrile (50 mL) was slowly added NBS (3.6 g, 20 mmol). After the addition of NBS was complete, the reaction mixture was heated at reflux with stirring for 2-3 h then left to cool to room temperature. The solvent was evaporated in *vacuo* and the residue was dissolved in chloroform (50 mL), washed with water (20 mL), and dried over MgSO₄. After evaporation of the solvent, the resulting solid was recrystallized from ethyl acetate to afford the bis(α -bromoketone) derivative **18** as colorless powder, (71%), mp 136 °C; IR (KBr) 1697 (C=O), 1659 (C=O) cm⁻¹; ¹H-NMR: δ 3.51 (d, 8H, NCH₂), 4.82 (s, 4H, CH₂Br), 5.03 (s, 4H, OCH₂), 7.05 (d, *J* 8.4 Hz, 4H, ArH), 7.96 (d, *J* 8.4 Hz, 4H, ArH); MS: *m/z* (%) 596 (M⁺). Anal. Calcd. for C₂₄H₂₄Br₂N₂O₆: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.33; H, 4.05; N, 4.67%.

Synthesis of 1,1'-(piperazine-1,4-diyl)bis(2-(4-(2-(2-(4-nitrobenzylidene)hydrazineyl)thiazol-4-yl)phenoxy)ethan-1-one) (25). To a solution of the piperazine bis(α -bromoketone) **18** (1 mmol) in ethanol (25 mL) containing TEA (0.2 mL), the *para* nitro benzaldehyde thiosemicarbazone (**24**) (2 mmol) was added. The reaction mixture was heated at reflux for 4 h. The obtained solid products upon cooling were filtered off and then recrystallized from ethanol/DMF to afford compounds **25** as red powder (87%), mp >300 °C; IR (cm⁻¹): 3298 (NH), 1665 (C=O); ¹H-NMR (DMSO): δ 3.349 (d, 8H, -NCH₂-), 4.88 (s, 4H, -OCH₂-), 6.95 (d, *J* 7.5 Hz, 4H, ArH), 7.21 (s, 2H, thiazole-5-H), 7.74 (d, *J* 7.5 Hz, 4H, ArH), 7.85 (d, *J* 8 Hz, 4H, ArH), 8.07 (s, 2H, CH=N), 8.23 (d, *J* 8 Hz, 4H, ArH), 12.53 (s, 2H, NH); ¹³C-NMR: δ 45.6, 66.4, 106.1, 115.9, 124.6, 126.5, 127.2, 129.4, 130.2,

136.3, 143.2, 148.0, 160.6, 166.1, 173.3; MS: m/z (%) 846 (M^+). Anal. Calcd. For $C_{40}H_{34}N_{10}O_8S_2$: C, 56.73; H, 4.05; N, 16.54; ; S, 7.57. Found: C, 56.70; H, 4.04; N, 16.54; S, 7.56 %.

Supplementary Material

Copies of 1H and ^{13}C NMR spectra of new compounds are given in the supplementary material associated with this manuscript.

References

1. Zhang, R.-H.; Guo, H.-Y.; Deng, H.; Li, J.; Quan, Z.-S. *J. Enzyme Inhib. Med. Chem.* **2021**, *36* (1), 1165.
<https://doi.org/10.1080/14756366.2021.1931861>
2. Al-Ghorbani, M.; Bushra Begum, A.; Zabiulla, Z.; Mamatha, S. V.; Khanum, S. A. *Res. J. Pharm. Technol.* **2015**, *8* (5), 611.
<https://doi.org/10.5958/0974-360X.2015.00100.6>
3. Shaquiquzzaman, M.; Verma, G.; Marella, A.; Akhter, M.; Akhtar, W.; Khan, M. F.; Tasneem, S.; Alam, M. *Eur. J. Med. Chem.* **2015**, *102*, 487.
<https://doi.org/10.1016/j.ejmech.2015.07.026>
4. Tamayo, N. A.; Norman, M. H.; Bartberger, M. D.; Hong, F. T.; Bo, Y.; Liu, L.; Nishimura, N.; Yang, K. C.; Tadesse, S.; Fotsch, C.; et al. *J. Med. Chem.* **2015**, *58* (11), 4462.
<https://doi.org/10.1021/jm5018175>
5. Migliore, M.; Pontis, S.; Fuentes de Arriba, A. L.; Realini, N.; Torrente, E.; Armirotti, A.; Romeo, E.; Di Martino, S.; Russo, D.; Pizzirani, D.; et al. *Angew. Chem.* **2016**, *128* (37), 11359.
<https://doi.org/10.1002/ange.201603746>
6. Cao, X.; Zhang, Y.; Chen, Y.; Qiu, Y.; Yu, M.; Xu, X.; Liu, X.; Liu, B. F.; Zhang, L.; Zhang, G. *J. Med. Chem.* **2018**, *61* (22), 10017.
<https://doi.org/10.1021/acs.jmedchem.8b01096>
7. He, Y.; Xie, F.; Ye, J.; Deuther-Conrad, W.; Cui, B.; Wang, L.; Lu, J.; Steinbach, J.; Brust, P.; Huang, Y.; et al. *J. Med. Chem.* **2017**, *60* (10), 4161.
<https://doi.org/10.1021/acs.jmedchem.6b01723>
8. Sergeant, N.; Vingtdeux, V.; Eddarkaoui, S.; Gay, M.; Evrard, C.; Le Fur, N.; Laurent, C.; Caillierez, R.; Obriot, H.; Larchanché, P. E.; et al. *Neurobiol. Dis.* **2019**, *129*, 217.
<https://doi.org/10.1016/j.nbd.2019.03.028>
9. Ji, Q.; Deng, Q.; Li, B.; Li, B.; Shen, Y. *Eur. J. Med. Chem.* **2019**, *180*, 204.
<https://doi.org/10.1016/j.ejmech.2019.07.035>
10. Salem, M. E.; Fares, I. M. Z.; Ghozlan, S. A. S.; Abdel-Aziz, M. M.; Abdelhamid, I. A.; Elwahy, A. H. M. *J. Heterocycl. Chem.* **2022**, *59* (11), 1907.
<https://doi.org/10.1002/jhet.4525>
11. Ali, S. H.; Sayed, A. R. *Synthetic Communications*. Taylor & Francis 2021, pp 670–700.
<https://doi.org/10.1080/00397911.2020.1854787>
12. Alizadeh, S. R.; Hashemi, S. M. *Medicinal Chemistry Research*. Springer 2021, pp 771–806.
<https://doi.org/10.1007/s00044-020-02686-2>

13. Petrou, A.; Fesatidou, M.; Geronikaki, A. *Molecules* **2021**, *26* (11), 3166.
<https://doi.org/10.3390/molecules26113166>
14. Scott, K. A.; Njardarson, J. T. *Topics in Current Chemistry*. Springer 2018, pp 1–34.
https://doi.org/10.1007/978-3-030-25598-5_1
15. Sharma, P. C.; Bansal, K. K.; Sharma, A.; Sharma, D.; Deep, A. *European Journal of Medicinal Chemistry*. Elsevier 2020, p 112016.
<https://doi.org/10.1016/j.ejmech.2019.112016>
16. Pola, S. In *Scope of Selective Heterocycles from Organic and Pharmaceutical Perspective*; InTech Rijeka, Croatia, 2016; Vol. 1, pp 13–62.
17. Posso, M. C.; Domingues, F. C.; Ferreira, S.; Silvestre, S. *Molecules* **2022**, *27* (1), 276 . DOI: 10.3390/molecules27010276.
<https://doi.org/10.3390/molecules27010276>
18. Gontijo, V. S.; Viegas, F. P. D.; Ortiz, C. J. C.; de Freitas Silva, M.; Damasio, C. M.; Rosa, M. C.; Campos, T. G.; Couto, D. S.; Tranches Dias, K. S.; Viegas, C. *Curr. Neuropharmacol.* **2019**, *18* (5), 348.
<https://doi.org/10.2174/1385272823666191021124443>
19. Kerru, N.; Singh, P.; Koorbanally, N.; Raj, R.; Kumar, V. *Eur. J. Med. Chem.* **2017**, *142*, 179.
<https://doi.org/10.1016/j.ejmech.2017.07.033>
20. Alkhzem, A. H.; Woodman, T. J.; Blagbrough, I. S. *RSC Adv.* **2022**, *12* (30), 19470.
<https://doi.org/10.1039/D2RA03281C>
21. Hooshmand, S. E.; Ghadari, R.; Mohammadian, R.; Shaabani, A.; Khavasi, H. R. *ChemistrySelect* **2019**, *4* (40), 11893.
<https://doi.org/10.1002/slct.201903361>
22. Al-Jumaili, M. H. A.; Hamad, A. A.; Hashem, H. E.; Hussein, A. D.; Muhaidi, M. J.; Ahmed, M. A.; ALBANAA, A. H. A.; Siddique, F.; Bakr, E. A. *Journal of Molecular Structure*. Elsevier 2023, p 133970.
<https://doi.org/10.1016/j.molstruc.2022.133970>
23. Ghozlan, S. A. S.; Abdelmoniem, A. M.; Butenschön, H.; Abdelhamid, I. A. *Tetrahedron* **2015**, *71* (9), 1413.
<https://doi.org/10.1016/j.tet.2015.01.026>
24. WalyEldeen, A. A.; Sabet, S.; El-Shorbagy, H. M.; Abdelhamid, I. A.; Ibrahim, S. A. *Chem. Biol. Interact.* **2023**, *369*, 110297.
<https://doi.org/10.1016/j.cbi.2022.110297>
25. Salem, M. E.; Abdullah, A. H.; Zaki, M. E. A.; Abdelhamid, I. A.; Elwahy, A. H. M. *ACS Omega* **2024**, *9* (9), 10146.
<https://doi.org/10.1021/acsomega.3c06653>
26. Ragheb, M. A.; Abdelrashid, H. E.; Elzayat, E. M.; Abdelhamid, I. A.; Soliman, M. H. *J. Biomol. Struct. Dyn.* **2024**, DOI: 10.1080/07391102.2024.2316764.
<https://doi.org/10.1080/07391102.2024.2316764>
27. Elwahy, A. H. M.; Shaaban, M. R.; Abdelhamid, I. A. *Adv. Heterocycl. Chem.* **2024**, *143*, 227.
<https://doi.org/10.1016/bs.aihch.2023.11.003>
28. Abdelhamid, I. A.; Diab, H. M.; Mahmoud, N. E.; Elwahy, A. H. M.; Fares, I. M. Z. *Arkivoc* **2024**, *2024* (8), 202412209.
<https://doi.org/10.24820/ark.5550190.p012.209>
29. Sayed, O. M.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. *J. Heterocycl. Chem.* **2016**, *53*, 1113.

<https://doi.org/10.1002/jhet.2373>

30. Mekky, A. E. M.; Elwahy, A. H. M. *J. Heterocycl. Chem.* **2014**, *51* (S1), E34.

<https://doi.org/10.1002/jhet.2012>

31. Elwahy, A. H. M.; Ginidi, A. R. S.; Shaaban, M. R.; Mohamed, A. H.; Gaber, H. M.; Ibrahim, L. I.; Farag, A. M.; Salem, M. E. *Arkivoc* **2024**, 2024 (vii), 202412181.

<https://doi.org/10.24820/ark.5550190.p012.181>

32. Diab, H. M.; Salem, M. E.; Abdelhamid, I. A.; Elwahy, A. H. M. *RSC Adv.* **2020**, *10* (72), 44066.

<https://doi.org/10.1039/D0RA09025E>

33. Salem, M. E.; Ahmed, A. A.; Shaaban, M. R.; Shibl, M. F.; Farag, A. M. *Spectrochim. Acta - Part A Mol. Biomol. Spectrosc.* **2015**, *148*, 175.

<https://doi.org/10.1016/j.saa.2015.03.102>

34. Salem, M. E.; Ahmed, A. A.; Darweesh, A. F.; Kühn, O.; Elwahy, A. H. M. *J. Mol. Struct.* **2019**, *1176*, 19.

<https://doi.org/10.1016/j.molstruc.2018.08.031>

35. Fathi, E. M.; Sroor, F. M.; Mahrous, K. F.; Mohamed, M. F.; Mahmoud, K.; Emara, M.; Elwahy, A. H. M.; Abdelhamid, I. A. *ChemistrySelect* **2021**, *6* (24), 6202.

<https://doi.org/10.1002/slct.202100884>

36. Ibrahim, N. S.; Mohamed, M. F.; Elwahy, A. H. M.; Abdelhamid, I. A. *Lett. Drug Des. Discov.* **2018**, *15* (10), 1036.

<https://doi.org/10.2174/1570180815666180105162323>

37. Abdelwahab, R. E.; Ragheb, M. A.; Elwahy, A. H. M.; Abdelhamid, I. A.; Abdelmoniem, A. M. *J. Mol. Struct.* **2024**, *1307* (January), 137946.

<https://doi.org/10.1016/j.molstruc.2024.137946>

38. Elwahy, A. H. M.; Hammad, H. F.; Ibrahim, N. S.; Al-Shamiri, H. A. S.; Darweesh, A. F.; Abdelhamid, I. A. *J. Mol. Struct.* **2024**, *1307* (March), 137965.

<https://doi.org/10.1016/j.molstruc.2024.137965>

39. Salem, M. E.; Abdelhamid, I. A.; Elwahy, A. H. M.; Ragheb, M. A.; Alqahtani, A. sultan; Zaki, M. E. A.; Algethami, F. K.; Mahmoud, H. K. *Heliyon* **2024**, *10* (10), e31082.

<https://doi.org/10.1016/j.heliyon.2024.e31082>

40. Abdullah, A. H.; Ibrahim, N. S.; Algethami, F. K.; Elwahy, A. H. M.; Abdelhamid, I. A.; Salem, M. E. *J. Mol. Struct.* **2024**, *1302* (August 2023), 137506.

<https://doi.org/10.1016/j.molstruc.2024.137506>

41. Ragheb, M. A.; Mohamed, F. G.; Diab, H. M.; Ragab, M. S.; Emara, M.; Elwahy, A. H. M.; Abdelhamid, I. A.; Soliman, M. H. *Chem. Biodivers.* **2024**, *21* (4), e202301341.

<https://doi.org/10.1002/cbdv.202301341>

42. Saleh, F. M.; Hassaneen, H. M.; Abdelhamid, I. A.; Mohamed Teleb, M. A. *Tetrahedron Lett.* **2024**, *137* (December 2023), 154957.

<https://doi.org/10.1016/j.tetlet.2024.154957>

43. Salem, M. E.; Fares, I. M. Z.; Ghozlan, S. A. S.; Elwahy, A. H. M.; Abdelhamid, I. A. *Synth. Commun.* **2022**, *52* (19–20), 1981.

<https://doi.org/10.1080/00397911.2022.2122844>

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